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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/923,870	08/06/2001	Bernhard Palsson	PALSSN.002C1	1729

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EXAMINER	
ALLEN, MARIANNE P	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,870	PALSSON, BERNHARD	
	Examiner	Art Unit	
	Marianne P. Allen	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 49-65 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 49-65 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/22/04 has been entered.

Claims 24-48 have been cancelled and claims 49-65 have been newly added. Claims 49-65 are under consideration by the examiner.

Oath/Declaration

Submission of a supplemental oath on 4/15/04 is noted.

Claim Rejections - 35 USC § 112

Claims 49-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirements. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and/or as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is both a new matter and enablement rejection.

Basis for all of the new claims is stated to be at pages 6-8 of the specification. This is not agreed with. Pages 6-8 describe a procedure for creating metabolic genotypes from genomic

sequence data and a procedure for producing an *in silico* microbial strain from the metabolic genotype created by the former procedure. The second procedure includes creating a genome specific stoichiometric matrix.

Claim 49 as written differs from the disclosed method in at least the following ways. The method does not require that the DNA sequence of the microbial genome be obtained. (See for example Figure 1 at state 14.) The specification does not appear to contemplate a method where this is not performed.

Claim 49 further recites "function of said proteins relates to cellular metabolism." The specification does not appear to set forth the concept of "relates." While the specification does disclose the concept of determining genes "involved" in cellular metabolism, "relates" and "involved" do not appear to be synonymous concepts.

Claim 51 recites a particular subset of genes involved in cellular metabolism. The first full paragraph on page 8 discloses a subset of genes involved in cellular metabolism but is not limited to this set. It includes those involved in central metabolism, carbohydrate assimilation, vitamin and cofactor biosynthesis, etc. Carbohydrate metabolism does not appear to be disclosed. Claim 59 is considered to be new matter for the same reasons.

Claim 53 as written further differs from the disclosed method in at least the following ways. The method does not require that the biomass composition of the microbial organism be determined. (See for example Figure 2 at state 60.) The specification does not appear to contemplate a method where this is not performed. Claim 61 is considered to be new matter for the same reasons.

Finally, claim 53 does not require performing flux balance analysis to produce the *in silico* strain of the microbial organism. Note that the combining in the disclosure on pages 6-8 in describing Figure 2 at state 64 is the flux balance analysis (FBA) and not any type of general linear programming problem. The specification does not appear to contemplate a more generic method of combining the metabolic demand and uptake rate with the stoichiometric matrix to produce an *in silico* representation.

Basis for the methods of claims 57-61 is not seen, particularly repeating steps a) to d) and providing only metabolic genes (as opposed to selecting the subset that are metabolic genes from the ORF's found in the whole genome). Applicant is requested to point to page and line number for basis.

The specification as originally filed would not reasonably convey to one of ordinary skill in the art that the invention as presently claimed was contemplated.

To the degree that the claim 49 is intended to assign function to every open reading frame identified in the microbial genome, the specification is not enabling. Note that claim 49 requires "determining open reading frames of genes in said microbe." If an open reading frame has little or no homology to gene sequences encoding proteins of known function, there is no discussion or guidance as to what to do. Neither the claims nor specification speak to discarding or not including such sequences in the genome specific stoichiometric matrix. Note that claim 57, step (e) requires repetition until "the substrates, products and stoichiometry of the metabolic genes in said microbe are known" implying that all metabolic genes in the genome must be determined. The specification does not provide any guidance on the level of sequence homology required to

assign function. That is, if the homology is 10%, is this sufficient to assign function? As set forth in the prior Office action, it is maintained that the specification lacks guidance in setting forth reasonable means for assigning a function based on a homology comparison. Again, Edwards et al. (PNAS, 2000) and Edwards et al. (JBC, 1999) were published after the filing date and as such would not have been known in the art at the time of this invention to provide guidance to one practicing the claimed invention. Furthermore, while these references discloses assembling information regarding metabolic reactions from a variety of sources (literature, annotated databases), there is no explanation as to any criteria used to assign function based on a homology comparison. Applicant argues on pages 9-10 of the response that one of ordinary skill in the art could follow the teachings of the specification (none with respect to level of homology or other criteria required to assign function) along with what is well-known in the art regarding homology matching. Whatever commonly accepted rules for assigning function applicant is relying upon or are asserting are well-known are not provided. This argument requires that the person practicing the method as claimed use judgment, make independent decisions, and thus exercise inventive skill. This constitutes undue experimentation.

Claims 49 and 57 require being able to discriminate between a metabolic gene and a non-metabolic gene. This determination can be where the "assigned function of said proteins relates to cellular metabolism" (claim 49) or is "involved in cellular metabolism" (claim 51). However, these do not clearly demarcate those genes or ORFs intended to be included or excluded. Page 8 provides a non-limiting list as to what was intended and the degree of "involvement" is not made clear. As such, one of ordinary skill in the art would not have known exactly which sequences to include or exclude. From the perspective that any gene can affect the overall

function of the cell, most, if not all, genes could be considered to be involved in cellular metabolism. Applicant's arguments do not address the fact that the specification disclosure of the metes and bounds of "metabolic gene" is non-limiting and applicant does not provide a limiting definition well-known to one of ordinary skill in the art at the time of the invention for a "metabolic gene."

As set forth in the prior Office action, the specification does not provide guidance on how assignment of function would then provide the metabolic reaction of the candidate metabolic gene. That is, assigning the function of a kinase based upon homology does not provide the substrate and product of the reaction. The specification provides absolutely no guidance as to how these should be determined. While page 8, discusses reviewing biochemical literature and available experimental data, this is considered to require undue experimentation given the breadth of the claims which are directed to any microbe and appear to embrace all genes of the microbial genome.

Claims 54 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54 and 65 add the steps of performing a flux balance analysis; however, this does not further define the method of producing the *in silico* representation as the last step in claims 53 and 57, respectively, are to produce an *in silico* representation. Note that this is at odds with the specification at page 10, first full paragraph, and pages 12-13, bridging paragraph, where the

flux balance analysis (FBA) is performed in order to fully define the metabolic system (i.e. produce the *in silico* representation).

Claim Rejections - 35 USC § 102

Claims 49-51, 53-59, and 61-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Schilling et al. (Biotech. Prog., 15(3):288-295, May/June 1999, of record).

As the claims as presently written embrace new matter, applicant is entitled to only the instant filing date of 8/6/01 and not the filing date of parent application 09/243,022.

Schilling et al. discloses using flux balance analysis to produce an *in silico* representation of a microbe. A genome is sequenced, open reading frames assigned, and sequence similarity and homology used to assign metabolic function. All possible reactions for associated with the metabolic gene products are included in the analysis. (See abstract, Figures, and page 290.) Biomass composition, uptake rates, and maintenance requirements are determined (i.e. claims 53 and 61.) *E. coli* is specifically disclosed. Biosynthetic pathways that generate all the components of biomass are included (i.e. claims 51 and 59.) (See page 291.)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schilling et al. al. (Biotech. Prog., 15(3):288-295, May/June 1999, of record).

Schilling et al. is applied as above. The reference does not appear to specifically disclose homology searching using BLAST. However, BLAST would have been a well known and commonly used search tool for homology searching at the time of the invention as noted in the specification at page 7. As such, it would have been obvious to use BLAST in the method disclosed by Schilling et al.

Claims 49-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Blattner et al. (Science, 1997, of record), Pennisi (Science, 1997), Edwards et al. (Abstracts of Papers, American Chemical Society, 213(1-3):BIOT 50, San Francisco, April 13-17, 1997), and Pramanik et al. (Biotechnology and Bioengineering, 1997, of record).

Blattner et al. discloses the complete genome sequence of *E. coli*. ORFs were determined and function assigned based on homology to other sequences or previous characterization. BLAST was used for homology searching. (See page 1454.) Metabolic functional groups were determined. (See Table 4.)

Pennisi establishes that several microbial genomes would have been fully sequenced, ORFs determined, and function assigned based on homology or previous characterization. *E. coli* and *H. influenzae* are specifically mentioned.

Edwards et al. discloses flux balance analysis of a metabolic network for *H. influenzae* based on homology of putative proteins with those encoded by the known part of the *E. coli* genome. Stoichiometric information was used.

Pramanik et al. discloses a stoichiometric model of *E. coli* metabolism. Flux balance analysis is used. Biomass experimental data was included. Metabolic pathways are shown in Appendix A.

It would have been obvious to produce a stoichiometric matrix and *in silico* model of the microbes *E. coli* and *H. influenzae* according to Pramanik et al. using the known genome sequence, ORFs, and metabolic genes for these microbes as disclosed by Blattner et al. and Pennisi et al. (where function has been assigned by using homology and tools such as BLAST). Such models clearly would have been of interest and within the skill of the art to produce as seen by Edwards et al. One would have been motivated to produce the stoichiometric matrix and *in silico* model in order to better understand microbial metabolism and provide more robust models of metabolism.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Thursday, 5:30 am - 1:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne P. Allen 6/16/04
Primary Examiner
Art Unit 1631

mpa